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ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/587,569	CAPPOLA ET AL.	
	Examiner	Art Unit	
	STEPHEN KAPUSHOC	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *19-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-30 are pending.

Claims 19-30 remain withdrawn from examination as detailed in the Office Action of 06/26/2009.

Claims 1-18 are examined on the merits.

Please note: The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This Office Action is in reply to Applicants' correspondence of 09/21/2009.

Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put the application in condition for allowance. Any new grounds of rejection presented in this Office Action are necessitated by Applicants' amendments. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.

This Action is made **FINAL**.

Election/Restrictions
Note on the Claim Amendments and the Elected Invention

1. Applicant's election of the particular combination of genes with increased expression of UQCRB, BTF3, ST13, and CUL4A; the particular gene with decreased expression of CFLAR; and the particular EST of SEQ ID NO: 12 has been addressed on pages 4-5 of the Office Action of 06/26/2009. The claims amendments of 09/21/2009 have changed requirements of the claims (e.g. independent claims 1 and 13) such that they are no longer generic with regard to genes, but now require only the non-elected subcombination of the particular gene UQCRB. In the interest of customer service and compact prosecution the claims are examined in so far as the independent claims may encompass the elected gene combination of UQCRB, BTF3, ST13, and CUL4A as genes overexpressed in rejection (claim 1) and underexpressed in non-rejection (claim 13) where the elected combination is specifically recited in dependent

claims 2 and 14. It is noted that no claim is indicated as allowed in this Office Action. Prior to the allowance of any claim, subject matter that has not been re-joined with the elected subject matter will be required to be removed from the claims.

It is noted that claim 16 was indicated on page 2-3 of the previous Office Action of 06/26/2009 as withdrawn from examination as to a non-elected invention for requiring a non-elected combination of genes. In light of the amendments to the claims, claim 16 is rejoined for examination on the merits.

Withdrawn Claim Objections

2. The objection to claims for recitation of gene symbols, as set forth on page 3 of the Office Action of 06/26/2009, is **WITHDRAWN** in light of the amendments to the claims.

The objection to claims for recitation of non-elected subject matter, as set forth on page 3 of the Office Action of 06/26/2009, is **WITHDRAWN**; please note the recitation of non-elected subcombinations is addressed above in this Office Action.

New Claim Objection

3. Claim 10 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. In the instant case

dependent claim 10 requires a cardiac transplant, but this limitation is already present in the independent claim.

Withdrawn Objection to the Specification

4. The objections to the disclosure, as set forth on page 5 of the Office Action of 06/26/2009, are **WITHDRAWN** in light of the amendments to the specification.

Withdrawn Claim Rejections - 35 USC § 112 2nd ¶ - Indefiniteness

5. The rejection of claims 1-15, 17 and 18 under 35 USC 112 2nd ¶ as indefinite, as set forth on paged 4-5 of the Office Action of 06/26/2009, are **WITHDRAWN** in light of the amendments to the claims.

New Claim Rejections - 35 USC § 112 2nd ¶ - Indefiniteness

6. Claims 14-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 14 and 15 are unclear over recitation of the phrase "said underexpressed genes'" in each of claims 14 and 15. There is not proper antecedent basis for "underexpressed genes" in the claims. The rejected claims may be made more clear in this regard if amended to recite the phrase "the genes with diminished expression".

Claim 16 is unclear over recitation of the phrase 'cullin 4A (CFLAR)', where the recited gene name is not consonant with the recited gene symbol. It is thus unclear if the claim is intended to require cullin 4A or CFLAR.

Maintained Claim Rejections - 35 USC § 112 1st ¶ - Enablement Newly Applied to Claims as Necessitated by Applicants' Amendments

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the invention and breadth of the claims

The claims are drawn to methods for detecting human cardiac rejection generically comprising the analysis of expression in blood of at least four over expressed genes including UQCRB and at least one under expressed gene as compared to a standard.

The claims are drawn to methods particularly comprising (as consonant with the Election) analysis of expression of UQCRB, BTF3, ST13, CUL4A, CFLAR, and SEQ ID NO: 12.

The claims encompass the detection of any level of gene expression, and comparison to any profile used as a standard; for example expression that is increases as compared to any level.

The claims thus require knowledge of a correlation between any level of gene expression of any generic gene, in any tissue sample type, in any subject organism and the presence of tissue rejection of any tissue type.

Direction provided by the specification and working example

The instant specification provides an analysis of human gene expression peripheral blood samples (p.26-27) in three populations of cardiac transplant subjects: (1) non-rejecting transplants (control); (2) actively rejecting transplants (rejection); and (3) rejection subjects following immunosuppression treatment to alleviate rejection (post-rejection). The specification teaches that in an analysis of gene expression in 7 controls, 7 rejection, and 7 post-rejection subjects (p.27) using the Affymetrix HU133A array, 91 candidate genes demonstrating differential expression between rejecting and non-rejecting subjects were identified (p.28). The specification further teaches that 40 transcripts were selected for classification of samples using hierarchical clustering (p.32-33; Figure 3), and asserts that the 40 genes are disclosed in Table 2 of the specification.

Relevant to the breadth of the rejected claims, the specification does not teach an analyses of the reliability of classification methods using less than the complete set of genes analyzed for the cluster analysis.

State of the art, level of skill in the art, and level of unpredictability

While the state of the art and level of skill in the art with regard to the analysis of mRNA expressed in any sample is high, the unpredictability in associating any gene expression level with a phenotype such as tissue rejection as encompassed by the claims is higher.

Because the claims encompass detecting any level of gene expression in a sample from an individual and comparing that level to any control level or average level to determine an elevated or diminished level that is indicative of rejection or non-rejection, it is relevant to point out the unpredictability associated with gene expression in any individual. Cheung et al (2003) teaches that there is natural variation in gene expression among different individuals. The reference teaches an assessment of natural variation of gene expression in lymphoblastoid cells in humans, and analyzes the variation of expression data among individuals and within individuals (replicates) (p.422, last paragraph; Fig 1). The data indicates that, for example, expression of ACTG2 in 35 individuals varied by a factor of 17; and that in expression of the 40 genes with the highest variance ratios, the highest and lowest values differed by a factor of 2.4 or greater (Fig 3). Similarly, the prior art of Shalon et al (2001) teaches that preferably 20-50 different test individuals are assayed to obtain meaningful data showing a significant change in gene expression levels, and changes of gene expression of at least 2 fold and up to 100 fold or more are desirable for the comparison of gene expression levels between a case and control population (p.10 ¶156, ¶158). Finally, Whitney et al teaches that in the analysis of gene expression using microarrays there is

considerable intrinsic inter-individual variation in gene expression even in samples within the same environment (Fig 3).

In light of the unpredictability of correlating gene expression to a phenotype, as established above, it is further relevant to point out that even a profile consonant with the Election is not established to be reliably indicative of cardiac tissue rejection in humans when examined in blood samples. For example, while the text of the specification asserts that clustering analysis was performed with 40 gene markers disclosed in Table 2 (e.g.: p.32), Table 2 in fact appears to disclose only 33 genes (12 ESTs and 21 named genes). Further, there is no indication in the specification that a clustering analysis using only 4 genes (e.g.: four genes overexpressed in rejection, as encompassed by claim 2) would classify rejection or non-rejection samples with a significant reliability. Given the teachings of the references cited in this rejection, correlation of gene expression with a phenotype is a highly unpredictable endeavor, and without some indication in the specification, there is in fact no assurance that the minimal gene set, as consonant with the election, would be reliably indicative of cardiac rejection phenotype.

Quantity of experimentation required

A large and prohibitive amount of experimentation would be required to make and use the claimed invention. Such experimentation would require case:control analysis and replication of all the experimentation of the instant specification with the minimal gene sample set as consonant with the Election. Even if such experimentation

were to be performed, there is no assurance that the relationships as required by the instantly claimed methods would be confirmed.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the lack of guidance by the applicant and the particular examples, it is the conclusion that an undue amount of experimentation would be required to make and use the claimed invention.

The Examiner has set forth, in part, that the claimed methods are not enabled with regard to the specifically elected gene set. In the event that Applicants may provide a Declaration or some other evidence that the methods are enabled with regard to the Elected gene set, the Examiner would suggest the following as exemplary claim language:

> A method for identifying cardiac transplant tissue rejection in a human subject, said method comprising:
>
> determining a first gene expression profile in a blood sample taken from said human subject, wherein said first gene expression profile comprises abundances of UQCRB, BTF3, ST13, CUL4A, and CFLAR mRNA; and
>
> comparing said first gene expression profile to a second gene expression profile, wherein said second gene expression profile comprises the abundances of UQCRB, BTF3, ST13, CUL4A, and CFLAR mRNA in blood samples from a human cardiac transplant population that does not have cardiac tissue rejection;
>
> wherein a statistically significant increase in UQCRB, BTF3, ST13, CUL4A mRNA abundance in said first gene expression profile compared to said second gene expression profile, and a statistically significant decrease in CFLAR mRNA abundance in said first gene expression profile compared to said second gene expression profile, is indicative of cardiac transplant tissue rejection in the human subject.

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 112 1st ¶ for lack of enablement. Applicants' arguments (p.12-15 of the Remarks of 09/21/2009) have been fully and carefully considered but are not found to be persuasive.

Initially it is noted that in light of the amendments to the claims, the portions of the rejection as set forth in the previous Office Action regarding the breadth of the claims as they encompass non-human subjects, rejection of non-cardiac tissue, and expression in non-blood samples, have been withdrawn from the rejection as set forth in the instant Office Action.

Applicants have argued (p.12 of Remarks), that the specification demonstrates multiple methods of determining an amount of gene expression, and thus it would be merely routine for the skilled artisan to identify a standard value for comparison. The argument is not persuasive. The instant methods are not drawn to methods of establishing control values or developing baseline expression values; the instant methods are methods of prediction which require that the artisan practicing the methods has an indication of the reliability of the method. As set forth in the rejection, there is no clear indication in the specification that an analysis of expression comprising only the elected genes is in fact suitable for prediction of rejection.

Applicants further argue (p.12-13 of Remarks) that the specification describes statistical tools for analyzing populations and comparing gene expression values. However, the portions of the specification cited in the Remarks do not offer evidence of enablement of the Elected invention. For example the specification at p.28 line 20 provides only an analysis of the selection of 91 candidate genes, where the elected

invention requires far fewer genes, and the genes required of the elected invention are not in fact established by the specification to be statistically sufficient to predict rejection. Furthermore, where Applicants have cited portions form pages 9 and 10 of the specification, the cited portions demonstrate the breadth of the claims where, the cited portions provide that standard for comparison may be derived from only a single subject. And while applicants argue (p.14 of the Remarks) that only the most basic and routine task would be required to obtain a standard value, the more relevant point with regard to the rejection and the claimed methods is that there would be an undue amount of experimentation associated with establishing whether or not such a standard, requiring at most the gene s of the Election, would be robust and reliable in comparisons for predicting cardiac rejection.

The rejection as set forth is **MAINTAINED.**

Withdrawn Claim Rejections - 35 USC § 102

9. The rejection of claims under 35 USC 102, as set forth on pages 12-13 of the Office Action of 06/26/2009, are **WITHDRAWN** in light of the amendments to the claims.

Conclusion

10. No claim is allowed

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action

is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached at 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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/Stephen Kapushoc/
Primary Examiner, Art Unit 1634